

PATENT COOPERATION TREATY

12 JAN. 2009

REQU - RECEIVED

ONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

882
cc CL
AOT.
LE CLOS DU GOLL
69, Rue Saint Simon
42000 St Etienne
FRANCE

Alexander J.

(PCT Rule 44.1)

Date of mailing
(day/month/year)

13/01/2009

Applicant's or agent's file reference

E56 PAT 2050W0

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/IB2008/000944

International filing date
(day/month/year)

17/04/2008

Applicant

PLANT RESEARCH INTERNATIONAL B.V.

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Julia Severin

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1 bis(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43bis.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference E56 PAT 2050WO	FOR FURTHER ACTION <small>see Form PCT/ISA/220 as well as, where applicable, item 5 below.</small>	
International application No. PCT/IB2008/000944	International filing date (day/month/year) 17/04/2008	(Earliest) Priority Date (day/month/year) 17/04/2007
Applicant PLANT RESEARCH INTERNATIONAL B.V.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 8 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☒ **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. 1
☒ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2008/000944

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
- a. type of material
- ☒ a sequence listing
- ☐ table(s) related to the sequence listing
- b. format of material
- ☒ on paper
- ☒ in electronic form
- c. time of filing/furnishing
- ☐ contained in the international application as filed
- ☐ filed together with the international application in electronic form
- ☒ furnished subsequently to this Authority for the purpose of search
2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2008/000944

A. CLASSIFICATION OF SUBJECT MATTER

INV. C12N15/82 A01H5/00 C07K14/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C12N A01H C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE, BIOSIS, WPI Data, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>WO 01/31045 A (STICHTING DIENST LANDBOUWKUNDI [NL]; BAKKER HENDRIKUS ANTONIUS CORN [N] 3 May 2001 (2001-05-03) cited in the application abstract page 4, line 10 - line 35 page 5, line 1 - line 33 page 9, line 9 - line 26 ----- -/--</p>	1-65, 122-124



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

18 September 2008

Date of mailing of the international search report

13/01/2009

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040,
 Fax: (+31-70) 340-3016

Authorized officer

Mundel, Christophe

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2008/000944

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>BAKKER H ET AL: "Galactose-extended glycans of antibodies produced by transgenic plants"</p> <p>PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE, WASHINGTON, DC, US, vol. 98, no. 5, 27 February 2001 (2001-02-27), pages 2899-2904, XP002226729</p> <p>ISSN: 0027-8424</p> <p>abstract</p> <p>page 2899, right-hand column, line 28 - line 35</p> <p>page 2904, left-hand column, line 1 - right-hand column, line 18</p> <p>-----</p>	1-65, 122-124
Y	<p>DATABASE UniProt</p> <p>Beta-1,4-galactosyltransferase (chicken)</p> <p>1 November 1996 (1996-11-01), SHAPER J.H.:</p> <p>XP002449280</p> <p>retrieved from EBI</p> <p>Database accession no. Q92074</p> <p>abstract</p> <p>-----</p>	1-65, 122-124
Y	<p>DATABASE EPO PROTEINS Chicken</p> <p>beta-1,4-galactosyltransferase</p> <p>20 May 2004 (2004-05-20), HILLMAN J.L. ET AL.:</p> <p>XP002449281</p> <p>retrieved from EBI</p> <p>Database accession no. ADL27179</p> <p>abstract</p> <p>-----</p>	1-65, 122-124
Y	<p>DATABASE EMBL Gallus gallus</p> <p>beta-1,4-galactosyltransferase</p> <p>3 August 1996 (1996-08-03), SHAPER J.H.:</p> <p>XP002449282</p> <p>retrieved from EBI</p> <p>Database accession no. U19890</p> <p>abstract</p> <p>-----</p>	1-65, 122-124
A	<p>DATABASE EMBL Danio rerio zgc:154116 mRNA</p> <p>5 August 2006 (2006-08-05), XP002449283</p> <p>retrieved from EBI</p> <p>Database accession no. BC124813</p> <p>abstract</p> <p>-----</p> <p style="text-align: center;">-/-</p>	1-65, 122-124

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2008/000944

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE UniProt Danio rerio galactosyl transferase 2 31 October 2006 (2006-10-31), STRAUSBERG ET AL.: XP002449284 retrieved from EBI Database accession no. Q08B99 abstract</p>	<p>1-65, 122-124</p>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2008/000944

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see annex

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-65, 122-124 (all completely)

A process for the production of a transgenic plant which is capable of adding beta-1,4-linked galactose residues to N-linked glycans comprising insertion of a nucleic acid molecule coding for the chicken beta-1,4-galactosyl transferase 1. A nucleic acid molecule encoding the chicken beta-1,4-galactosyltransferase extended at its N-terminus with an amino acid sequence corresponding to the N-terminal 10-20 amino acids sequence of a mammalian beta-1,4-galactosyltransferase causing the modified enzyme to be localized in trans-Golgi membranes, a vector or host cell comprising such a nucleic acid, a plant containing such a cell and a method for the production of a protein comprising a galactosylated N-linked glycan using a transgenic plant comprising such a nucleic acid.

2. claims: 66-121 and 125-127 (all completely)

A process for the production of a transgenic plant which is capable of adding beta-1,4-linked galactose residues to N-linked glycans comprising insertion of a nucleic acid molecule coding for the zebrafish beta-1,4-galactosyl transferase 1. A nucleic acid molecule encoding the zebrafish beta-1,4-galactosyltransferase extended at its N-terminus with an amino acid sequence corresponding to the N-terminal 10-20 amino acids sequence of a mammalian beta-1,4-galactosyltransferase causing the modified enzyme to be localized in trans-Golgi membranes, a vector or host cell comprising such a nucleic acid, a plant containing such a cell and a method for the production of a protein comprising a galactosylated N-linked glycan using a transgenic plant comprising such a nucleic acid.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2008/000944

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0131045	A	03-05-2001	AT 365219 T 15-07-2007
		AU 1738401 A	08-05-2001
		BR 0015031 A	18-06-2002
		CA 2389217 A1	03-05-2001
		DE 60035285 T2	21-02-2008
		DK 1228231 T3	29-10-2007
		ES 2288882 T3	01-02-2008
		JP 2003512076 T	02-04-2003
		MX PA02004142 A	20-08-2003
		NZ 518532 A	27-02-2004
		TR 200201121 T2	21-01-2003
		US 2008003680 A1	03-01-2008

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/IB2008/000944

International filing date (day/month/year)
17.04.2008

Priority date (day/month/year)
17.04.2007

International Patent Classification (IPC) or both national classification and IPC
INV. C12N15/82 A01H5/00 C07K14/00

Applicant
PLANT RESEARCH INTERNATIONAL B.V.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Mundel, Christophe

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2008/000944

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ on paper
 - ☒ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☒ furnished subsequently to this Authority for the purposes of search.
4. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/B2008/000944

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

- ☐ the entire international application
- ☒ claims Nos. 66-121, 125-127

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):
- ☒ no international search report has been established for the whole application or for said claims Nos. 66-121, 125-127
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
 - ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
 - ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
 - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See Supplemental Box for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2008/000944

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-65, 122-124 (all completely)

Box No. V Reasoned statement under Rule 43b/s.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-43, 46-65, 122-124</u>
	No: Claims	<u>44-45</u>
Inventive step (IS)	Yes: Claims	<u>39-42</u>
	No: Claims	<u>1-38, 43-65, 122-124</u>
Industrial applicability (IA)	Yes: Claims	<u>1-65, 122-124</u>
	No: Claims	

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2008/000944

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The present application lacks unity. Since the Applicant has elected not to pay the additional search fee, only the claims corresponding to the first invention have been searched (see point IV below). Therefore, only claims 1-65 and 122-124 will be the subject of the present opinion.

Re Item IV

Lack of unity of invention

This Authority considers that there are 2 inventions covered by the claims indicated as follows:

I: Claims 1-65 and 122-124 :

A process for the production of a transgenic plant which is capable of adding beta-1,4-linked galactose residues to N-linked glycans comprising insertion of a nucleic acid molecule coding for the chicken beta-1,4-galactosyltransferase 1. A nucleic acid molecule encoding the chicken beta-1,4-galactosyltransferase extended at its N-terminus with an amino acid sequence corresponding to the N-terminal 10-20 amino acids sequence of a mammalian beta-1,4-galactosyltransferase causing the modified enzyme to be localized in trans-Golgi membranes, a vector or host cell comprising such a nucleic acid, a plant containing such a cell and a method for the production of a protein comprising a galactosylated N-linked glycan using a transgenic plant comprising such a nucleic acid.

II: Claims 66-121 and 125-127 :

A process for the production of a transgenic plant which is capable of adding beta-1,4-linked galactose residues to N-linked glycans comprising insertion of a nucleic acid molecule coding for the zebrafish beta-1,4-galactosyl transferase 1. A

nucleic acid molecule encoding the zebrafish beta-1,4-galactosyltransferase extended at its N-terminus with an amino acid sequence corresponding to the N-terminal 10-20 amino acids sequence of a mammalian beta-1,4-galactosyltransferase causing the modified enzyme to be localized in trans-Golgi membranes, a vector or host cell comprising such a nucleic acid, a plant containing such a cell and a method for the production of a protein comprising a galactosylated N-linked glycan using a transgenic plant comprising such a nucleic acid.

The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

The problem to be solved by the present application can be seen as the provision of transgenic plants expressing heterologous β -1,4-galactosyltransferases.

The present application provides (at least) two solutions to this problem :

1. Transgenic plants expressing the chicken β -1,4-galactosyltransferase 1.
2. Transgenic plants expressing the zebrafish β -1,4-galactosyltransferase 1.

The common concept linking the two groups of inventions mentioned above can be seen as the provision of transgenic plants expressing an **animal** beta-1,4-galactosyltransferase.

However, each of D1 and D2 already disclose transgenic plants expressing a **mammalian** β -1,4-galactosyltransferase and more particularly **human** β -1,4-galactosyltransferase 1.

Therefore, the common concept linking the two groups of invention cannot be seen as novel (Article 33(2) PCT) or inventive (Article 33(3) PCT). Consequently, and in the absence of any special technical feature within the meaning of Rule 13.2 PCT, the present application lacks unity (Rule 13.1 PCT) and each of the two above mentioned groups has to be considered as an independent invention.

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. The present application refers to processes for the production of transgenic plants or transgenic plant cells comprising the insertion of a nucleic acid encoding a chicken β -1,4-galactosyltransferase into the genome of a plant or plant cell. The application also refers to a nucleic acid molecule encoding a non-mammalian β -1,4-galactosyltransferase extended at its N-terminus with an amino acid sequence corresponding to the N-terminal 10-20 amino acids sequence of a mammalian β -1,4-galactosyltransferase causing the modified enzyme to be primarily localized in the trans-Golgi membranes, a vector containing such a nucleic acid, a host cell comprising such a nucleic acid or such a vector, a plant comprising such a nucleic acid or such a vector and to a method for the production of a protein comprising a galactosylated N-linked glycan.
2. Reference is made to the following documents :
 - D1: WO 01/31045 A (STICHTING DIENST LANDBOUWKUNDI [NL]; BAKKER HENDRIKUS ANTONIUS CORN [N] 3 May 2001 (2001-05-03) cited in the application
 - D2: BAKKER H ET AL: "Galactose-extended glycans of antibodies produced by transgenic plants" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE, WASHINGTON, DC, US, vol. 98, no. 5, 27 February 2001 (2001-02-27), pages 2899-2904.
 - D3: DATABASE UniProt Beta-1,4-galactosyltransferase (chicken) 1 November 1996 (1996-11-01), SHAPER J.H.: retrieved from EBI Database accession no. Q92074
 - D4: DATABASE EPO PROTEINS Chicken beta-1,4-galactosyltransferase 20 May 2004 (2004-05-20), HILLMAN J.L. ET AL.: retrieved from EBI Database accession no. ADL27179
 - D5: DATABASE EMBL Gallus gallus beta-1,4-galactosyltransferase 3 August 1996 (1996-08-03), SHAPER J.H.: retrieved from EBI Database accession no.

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3. Novelty; Article 33(2) PCT.

- 3.1 Due to the clarity problem mentioned in point VIII-11 below, the subject-matter of claim 44 cannot be considered as novel over glycoproteins produced by animal cells.
- 3.2 Due to the clarity problem mentioned in point VIII-12 below, the subject-matter of claim 45 cannot be considered as novel over parts of a normal plant.
- 3.3 None of the prior art documents discloses the generation of a transgenic plant comprising a chicken β -1,4-galactosyltransferase. Moreover, none of the prior art documents discloses a nucleic acid encoding a chicken β -1,4-galactosyltransferase extended at its N-terminus with an amino acid sequence corresponding to the N-terminal 10-20 amino acids of a mammalian β -1,4-galactosyltransferase.

Therefore, the subject-matter of claims 1-65 and 122-124 has to be considered as novel in the sense of Article 33(2) PCT.

4. Inventive step; Article 33(3) PCT.

The most relevant document for the evaluation of the inventive step of the claims is the document D1. D1 discloses the generation of transgenic plants expressing, inter alia, the human β -1,4-galactosyltransferase and the use of said plants for the production of antibodies.

In the light of this document, the problem to be solved by the present application appears to be the provision of further β -1,4-galactosyltransferases which can be used in the methods of D1.

The Application solves this problem by the provision of the chicken β -1,4-

galactosyltransferase shown in SEQ ID NO:2.

However, the document D3-D5 already disclose the existence of a chicken β -1,4-galactosyltransferase. The International Search Authority (ISA) is of the opinion that the skilled person, searching for an alternative β -1,4-galactosyltransferase to be used in the method of D1, would have considered using the chicken β -1,4-galactosyltransferase disclosed in documents D3 to D5.

The attention of the applicant is drawn to the fact that, in order to be considered as inventive, the selection of the specific chicken β -1,4-galactosyltransferase should be motivated by a technical purpose, i.e. a hitherto unknown or unexpected effect due to the choice of this specific enzyme. For the moment, the ISA fails to see such an effect for the selection of the chicken β -1,4-galactosyltransferase.

Another aspect of the present application is the use of the N-terminal amino acid sequence of a mammalian β -1,4-galactosyltransferase fused to the chicken β -1,4-galactosyltransferase in order to obtain a proper location of the protein in the Golgi apparatus.

The attention of the applicant is drawn to the fact that D1 already discloses the importance of the presence of the enzyme in the Golgi apparatus (p. 9, lines 9-12) and also discloses that the N-terminal cytoplasmic region, transmembrane and stem region of glycosyltransferase determine the localisation of the enzyme in the ER or Golgi membrane (p. 9, lines 20-22).

The document D2 discloses the fact that the human β -1,4-galactosyltransferase is located in the median and trans-Golgi compartments (p. 2903, right-hand column, line 23 to p. 2904, left-hand column, line 3).

Therefore, the skilled person would need no inventive activity to use the N-terminal region of human β -1,4-galactosyltransferase in order to target a protein in the trans-Golgi compartment.

Therefore, the ISA is of the opinion that claims 1-38, 43-65 and 122-124 of the present application lack an inventive step (Article 33(3) PCT).

Re Item VIII

Certain observations on the international application

Lack of clarity; Article 6 PCT.

1. The broad wording "non-mammalian β -1,4-galactosyltransferase" encompasses enzymes which are not of animal origin like bacterial enzymes. The ISA is of the opinion that such enzymes would not solve the problem to be solved by the present application.

The present application only refers to animal β -1,4-galactosyltransferases. Therefore, the subject-matter of claim 1 cannot be considered as supported over the whole scope of the claim (Article 6 PCT in combination with Article 5 PCT).

This remark also applies to claim 13

2. In claim 4, the amino acid sequence is only characterized by the result to be achieved by said sequence, i.e. "capable of directing localisation of the non-mammalian β -1,4-galactosyltransferase in the Golgi apparatus".
According to the PCT International Search and Examination Guidelines as in force from March 25, 2004, chapter 5.35 : "The area defined by the claims must be as precise as the invention allows. As a general rule, claims which attempt to define the invention, or a feature thereof, by a result to be achieved should be objected to as lacking clarity".
3. Claim 5 refers to the "N-terminal amino acid sequence of a mammalian β -1,4-galactosyltransferase 1". However, no length limit is set for said sequence which could extend from few amino acids up to the half of the protein. This renders the scope of claim 5 unclear.

This remark also applies to claims 49, 58 and 123.

4. In claim 6, it is not clear which amino acid sequence should comprise the sequence [K/R]-X-[K/R].
5. Claim 9 refers to a CTS which is derived from a mammalian Golgi-localized protein. The ISA considers that this wording is unclear since the nature of the derivation is not given.

It is also not clear for the ISA if all the Golgi-localized protein will have a CTS. If not, the Applicant is invited to precise the origin of the CTS.

These remarks also apply to claims 10-12, 33, 52-55, 57 and 124.

6. The wording "partially isolating" used in claim 14 is unclear.
7. The wording "essentially devoid" used in claim 16 is vague and renders the scope of the claim unclear.

This remark also applies to claims 17 and 18.

8. In claim 19, it is not clear what is meant by a "functional fragment" of an antibody. Moreover, it is not clear what is precisely meant by "vaccine".
9. Claim 27 refers to the "enzymatically active domain of the non-mammalian β -1,4-galactosyltransferase". It is not clear what this domain should precisely be since no limits are given for said domain in the claim.

This remark also applies to claims 28-30 and 58.

10. It is not clear what a "mammalian extension" according to claim 31 should precisely be, what renders the scope of the claim unclear.

Moreover, it is not clear where this extension should be located.

This remark also applies to claim 32.

11. It is not clear how a protein according to claim 44 should be distinguished from a glycoprotein produced by an animal cell line. Therefore, claim 44 cannot be considered as novel.
12. All the part of a transgenic plant will not necessarily comprise the transgene. Therefore, the subject-matter of claim 45 will not always be distinguishable from a part of a "natural" plant (i.e. not transformed by the nucleic acids of the present application).
13. Claim 56 refers to a amino acid sequence that comprises SEQ ID NO:11. It is not clear which amino acid sequence is meant what renders the claim unclear.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information	<p>For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.</p>
Amending claims under Art. 19 PCT	<p>Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.</p>
Filing a demand for international preliminary examination	<p>In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/ WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT).</p> <p>If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).</p>
Filing informal comments	<p>After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.</p>
End of the international phase	<p>At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).</p>
Relevant PCT Rules and more information	<p>Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003</p>